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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/826,069
Filing Date: April 04, 2001
Appellant(s): NAPARSTEK, YAAKOV

Debra Z. Anderson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/15/2010

appealing from the Office action mailed 3/17/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

U.S. Patent No. 6,228,363, 5/08/2001, Naparstek, Y.

Gaubitz, M., et al. *Prospective Randomized Trial of Two Different Immunosorbers in Severe Systemic Lupus Erythematosus*. J. Autoimmun. 1998; Vol. 11, Pages 495-501.

Madaio, M.P., et al. *Emerging Concepts Regarding B Cells and Autoantibodies in Murine Lupus Nephritis*. J. Am. Soc. Nephrol. 1996; Vol. 7, Pages 387-396.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaubitz et al. (1999) in view of U.S. Patent No. 6,228,363 and Madaio et al. (1996).

Gaubitz, M., et al. teaches a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies. The reference further teaches that dsDNA-Ab play a "pivotal" role in the pathogenesis of SLE and that their removal proved useful for the treatment of the disease (see particularly Introduction and Discussion).

The reference teaching differs from the claimed invention only in that it does not teach a method employing a column comprising the R38 peptide nor the use of a Sepharose™ column.

The '363 patent teaches that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies (see particularly column 3, lines 13-19).

Madaio et al. teaches that dsDNA-Ab from lupus patients also recognize laminin (see particularly Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies, as taught by Gaubitz et al., employing the R38 peptide of the '363 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to employ the R38 peptide on an immunoadsorption column given the teachings of Madaio et al. that dsDNA-Ab from lupus patients also recognize laminin and the '363 patent that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies. Note that Claim 8 is included in the rejection because various types of immunoadsorber matrices (including Sepharose™) for column chromatography were well-known in the art at the time of the invention. The choice of any particular immunoadsorber matrix would have comprised only routine optimization of the claimed method and would have been well within the purview of one of ordinary skill in the art at the time of the invention. Note that claim 10 does not recite

any new limitations because all ligands are coupled to Sepharose™ in some sort of "coupling buffer" (an ordinarily skilled artisan would know that Sepharose™ could not used in a dry form for column chromatography because column chromatography employs the flow of liquid through the column). Further, the extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies was known in the art. Substituting a ligand known to bind said pathogenic antibodies for the ligand of the primary reference would have been expected function for the binding and removal of said pathogenic antibodies from the plasma.

(10) Response to Argument

Appellant begins in Section **A.** with a summary of the Examiner's rejection and response to previous Appellant arguments. Note that this is only a summary; it does not comprise the complete Examiner's rejection and response to arguments set forth in the Final Office action of 3/17/09.

In Section **B.** Appellant summarizes the prior art. Again, Appellant's summary does not comprise the complete teachings of the references.

In Section **C.** Appellant begins arguments. Specifically, Appellant argues, "[T]he Examiner refuses to give adequate consideration to 1) the differences between the present invention and the prior art; 2) the data presented in the declarations of Dr. Naparstek, including evidence of unexpected results; and 3) evidence of failure of others. All of these

together point to a lack of predictability or expectation of success and are sufficient to overcome any so-called *prima facie* case of obviousness. Appellant addresses each of these factors in turn, and respectfully requests reconsideration".

Regarding Appellant's first point, the differences between the present invention and the prior art, Appellant describes some of the differences, but a careful reading of the section reveals little actual argument. For example, Appellant states, "In sum, there are no (emphasis by Appellant) references cited by the Examiner showing extracorporeal methods of removing antigen-specific antibodies for treatment of any (emphasis by Appellant) disease." While this statement may be true, it is unclear how this routine and obvious procedure, i.e., the routine and obvious removal of antigen-specific antibodies from a solution, would be patentably distinct. As set forth above, the affinity purification of antibodies, i.e., the purification of antibodies employing their specific affinity for antigen, has been routine for decades. While Appellant may argue that "[T]he present invention is the first method of treatment of SLE using extracorporeal removal of only lupus specific-autoantibodies, and is one of the first attempts at antigen-specific extracorporeal removal of antibodies in the treatment of disease", the claimed method would never the less have been routine and obvious.

At this point, at page 19 of the Brief, Appellant abandons the three point numbering system set forth at the top of page 18 of the Brief, now arguing as a second point a lack of expectation of success. Note that Appellant, "[D]oes not deny

that antibody-antigen interactions, in general, are well-characterized, and also acknowledges that as a general proposition anti-R38 antibodies would be expected to bind to R38." Appellant asserts that the claimed method, "[I]s a method of treating a patient" (emphasis by Appellant) and not a "laboratory method". But, as Appellant fails to pursue the assertion, it is unclear what Appellant considers to be the difference. Laboratory methods and procedures are routinely used in clinical medicine. Appellant asserts that, "[T]here was no guarantee that the same binding shown on an ELISA plate (as described in the '363 patent) will occur in a column, due to conformational changes in the protein when attached to a substrate, particularly a protein that is only twenty-one amino acids in length." This assertion lacks sound scientific reasoning. The very fact that the antigen is a short peptide, as opposed to a full-length three-dimensional protein, would render the possibility of a conformational epitope, i.e., a three-dimensional epitope based on non-contiguous amino acids, next to impossible, certainly beyond the realm of reasonable expectation. Note that Appellant offers no evidence that there would have been any reason to expect a difference in binding capability of a linear peptide on a column as opposed to an ELISA plate. And of particular note is the Inventor's teaching in the '363 patent that ELISA is just a routine and interchangeable method of binding anti-R38 antibodies See particularly the teachings of column 3, lines 52-57, "Detection of R38-binding antibodies may be undertaken by any method known by one skilled in the art. Examples of such methods of detection include ELISA and variations thereon, chemiluminescent techniques, etc. The actual method of detection is not crucial

to the success of the assay." Clearly this cite, in the Inventor's own patent, shows that there was no expectation that the system used to bind an anti-R38 antibody would have been expected to have any influence on said binding. As for the Appellant's assertion that the unpredictability of the, "[E]ntire system" is "[C]onveniently overlooked", Appellant has presented no persuasive argument that any aspect of the claimed method actually is anything other than routine employing decades old tried-and-true methods.

Appellant turns to a selective review of the declarations of Inventor Naparstek. Note that Appellant has confusingly chosen to refer to the declarations as "first" through "fourth", even though the declarations are not so numbered, rather than by date of submission. For clarity, the "first" declaration is the declaration submitted 6/22/05, the "second" is the declaration submitted 9/24/07, the "third" is the declaration submitted 12/10/07, and the "fourth" is the declaration submitted 6/29/08.

Appellant asserts that the second declaration indicates successful treatment of a single patient and an unexpected continued decline in lupus autoantibodies.

First, the treatment of a single patient reveals very little. Any results obtained on such a tiny patient sample must be considered little more than anecdotal. Second, it is unclear how the results obtained on the single patient can be considered

to be unexpected as they were not compared to any other results. Also note that the "attached chart" referred to in the declaration has not been found in the Appeal Brief.

Appellant states, "In seven of the ten patients shown in the Fourth Declaration, the treatment regimen was successful, and no rebound effect was observed. These results are, in fact, statistically significant (p.01), as indicated in Figure 11 in the declaration. The patient data shown in Figures 1, 7, 8, 9, 10, 11 also exhibit a continued decline in autoantibody levels measured post-treatment".

Appellant's conclusions based on the declaration and the data presented therein are, at best, highly selective. First, the "statistically significant" results reported in the declaration were obtained for just 2 of 5 post-treatment visits. Accordingly, the results were not significant for the majority of post-treatment visits. Further, while the Inventor could declare that "[N]o rebound effect was observed", what then should the increased antibody levels in Figures, 1, 3, 4, possibly 5, and 6 be referred to as? And how can the Appellant assert that the autoantibody levels in Figure 1 "continued to decline" when they were significantly above the starting level by Visit 5?

Appellant asserts that the third declaration explains the "well-known" phenomenon, "When antibodies are removed by

plasmapheresis, a rebound effect occurs, usually within 7-10 days [emphasis by Appellant] (see Reference 2 in the Fourth Declaration), and serum levels of antibodies spike higher than the levels measured just prior to the plasmapheresis treatment. In seven of the ten patients shown in the Fourth Declaration, the treatment regimen was successful, and no rebound effect was observed."

A review of the declaration and references reveals that Appellant's characterization is not accurate. The Declarant refers to a rebound effect citing Graninger et al. (2002) and Gokhale et al. (2001) in support. But Graninger et al. merely refers to "[A] *hypothetical* rebound synthesis of autologous immunoglobulin" (page 29, emphasis added) without any further comment. And regarding Gokhale et al., it must first be noted that the complete reference has never been made of record, only an Abstract has been submitted. A review of this single short paragraph, however, shows that the authors report only, "Rebound *flare* of disease activity noted in two patients between 7^{th}-10^{th} day requiring additional immunosuppressants or steroids" (emphasis added). There is no report that this "flare" comprises an antibody rebound effect nor is there any report that any effect "usually" occurs with 7-10 days as is asserted by the Appellant. Thus, Appellant has grossly mischaracterized the teachings of this reference.

Appellant argues that, "[T]here is no scientific basis or rationale provided for the Examiner's inference that removal of

only pathogenic antibodies will avoid the rebound effect. Removal of pathogenic antibodies alone *could have* induced a rebound in the levels of pathogenic antibodies. On the other hand, the opposite *could have* happened, and this was what, in fact, was observed in the present invention. No reference or citation to other scientific fact was provided for the assertion that it was entirely predictable that no rebound would occur."

Sound scientific reasoning requires the expectation of the probable before the expectation of the improbable. In this instance sound scientific reasoning would lead the ordinarily skilled artisan to expect that a rebound effect would be much less likely if only a small percentage of plasma antibodies were removed than if all plasma antibodies were removed.

Appellant states, "It is asserted by the Examiner that the continued decline of antibody levels post-treatment is not unexpected. … As with many other assertions in the Office Action, these are the Examiner's conclusory statements made without any factual foundation whatsoever".

Appellant has mischaracterized the Examiner's position which is that unexpected results have not been properly demonstrated. Regarding the Examiner's "many other "assertions" and "conclusory statements made without any factual foundation whatsoever", Appellant has not chosen to elucidate upon them

thus, these asserted "assertions" and "conclusions" cannot be addressed here.

Appellant states, "Finally, it is asserted in the Final Rejection that evidence of unexpected results must "properly appear in the specification" and can therefore be disregarded if not in the application as filed. Citation to *In re Davies and Hopkins*, 177 USPQ 381 (CCPA 1973) is provided as support for this position."

Appellant has again mischaracterized the Examiner's actual position. As set forth in the rejection of 12/13/07 at page 3, "It is well established that the assertion of unexpected properties in the course of prosecution is not as persuasive as when said results are disclosed in the specification." It has never been the position of the Examiner that evidence of unexpected results "must" appear in the specification, only that it is more persuasive if it does.

Appellant cites *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385, 70 USPQ2d 1957 (Fed. Cir. 2004).

The issue of *Knoll v. Teva* was addressed in the rejection of 9/17/087:

Regarding *Knoll v. Teva,* the fact pattern in the case is quite different from that in the instant case. First, the application *did* cite surprising results (which is not the case here). Second, the issue was technical in nature, i.e., whether or not a summary judgment by a district court was proper (it was not). Third, the court ruled regarding the new submission of unexpected results in "response to a litigation attack", not in the prosecution of a patent application. Finally, the court simply reversed and remanded the case to the district court for further review.

Appellant continues in the instant Brief asserting the "Failure of Others", citing Hershko and Naparstek (2005).

This reference was addressed in the rejection of 3/17/09:

The introduction of the reference teaches, "Until two decades ago, therapeutic plasma exchange was the only procedure used for antibody removal from the plasma", followed by a review of newer methods designed to remove only specific pathogenic antibodies. This teaching demonstrates that the removal of antibodies from the blood for the treatment of certain diseases is a very well-known concept. The reference continues by discussing the methods as they are used in the treatment of three diseases, MG, DCM, and SLE.

Applicant argues that treatment of MG by the removal of specific antibodies was unsuccessful.

Applicant's position is acknowledged. However, a review of the reference reveals that the apparent failure of the method in the context of MG was due to the low affinity of a single peptide for a single antibody. Contrast that with the successes in treating SLE. At page 637 the reference teaches that in one method anti-dsDNA complexes were eliminated and inflammation was ameliorated. Note that anti-dsDNA antibodies are the ligand for the R38 peptides employed in the method of the instant claims. Also see pages 640-641 wherein the authors teach that SLE can be effectively treated through the removal of anti-dsDNA antibodies, e.g., the quality of life of SLE patients improved due to a reduction in anti-dsDNA antibodies after being administered LJP394. Indeed, the reference supports the Examiner's position of obviousness in stating, "Peptide-bound columns allow specific removal of the pathogenic antibodies, implying that extracorporeal specific immunoadsorption on the laminin-epitope columns may serve as a new therapeutic alternative for SLE".

The position of the authors seems to be one of guarded optimism with the major concern being that pathogenic autoantibodies need to be identified before the method can be used. But fortunately, with SLE, pathogenic autoantibodies have been identified. The authors teach that it is the anti-dsDNA antibodies that are involved with renal disease that are pathogenic in the disease. While direct evidence might be lacking, the fact that the method of reducing levels of anti-dsDNA antibodies has been demonstrated to treat the disease is enough to render the method of the instant claims obvious in view of the prior art.

Appellant continues in the instant Brief by asserting that the optimism of the reference, "[I]s referring to the inventor's success in the present invention, and does not in any way support the Examiner's position". Appellant concludes, "Apparently, the publication date of this reference was overlooked. Again, the Examiner refuses to give adequate (or any) consideration to evidence provided by Appellant."

The Appellant's conclusion seems gratuitous in the face of the actual teaching of the reference. At pages 640-641 the reference first teaches LJP394-antigen-specific therapy which was not the Inventor's own invention, and indeed, pre-dated the Inventor's use of antigen-specific therapy. Only after two paragraphs describing the use of LJP394 does the Inventor discuss his own antigen-specific therapy in the final paragraph of the section on SLE. As regards Appellant's final statements, they do not bear address as they appear to be only inflammatory in nature.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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